

## REMARKS

In the outstanding Office Action, claims 1-28 and 31-32 were presented for examination. Claims 1-28 and 31-32 were provisionally rejected for double patenting under 35 USC §103 over claims 1-20 of application number 10/469,747. Claims 5, 7 13, 20 and 22 were rejected under 35 U.S.C. §112 second paragraph as being indefinite and claims 1-7, 9-14, 18-22, 24-27 and 31-32 under 35 USC §112 first paragraph as failing to comply with the written description requirement. In addition, rejection was advanced on the basis of 35 U.S.C. §103 against claims 1-28, 31 and 32 as being unpatentable over Chang et al. in view of Olsen et al.

The Office Action has been most carefully studied. In this amendment, base claims 1, 2 and 10 have been amended. Accordingly, as will be discussed in detail below, it is believed that the application is clearly in condition for allowance.

### *Withdrawal of Rejections*

The withdrawal of the rejection of claim 3 and of anticipation rejections based on Change et al. are appreciated.

### *Claim Amendments*

Base claims 1, 2 and 10 have been amended, without narrowing, to make explicit subject matter that was inherent prior to the amendment namely that the claimed plasma substitute or expander composition has a low blood clearance rate. This explicit recitation helps highlight the a distinctive feature of the claimed invention namely that the plasma substitute or expander composition claimed or provided has a low clearance rate from the blood circulation so that its beneficial effects persist longer.

### *Double Patenting*

The claims of the present application are believed clearly and patentably distinguished from the claims of copending application number 10/469,747. The claims of the copending application are directed to a plasma substance composition, and its use, in which less than 2% of the amino acid residues of the composition are hydroxyproline residues. As described, for example, at page 1 [0008] of US2005/0119170, the publication document of 10/469,747, the invention claimed in the copending application can reduce the risk of immunological reactions.

In contrast, base claims 1, 2 and 10, and consequently all pending claims in the present application, are limited to a composition or method of providing same comprising a recombinant gelatin-like protein having an isoelectric point less than 8, which solves the problem in the art of unduly rapid blood clearance rates, as is described in the specification herein for example at page 10, lines 28-30 of the specification herein. The claims of 10/469,747 do not remotely suggest that the problem in the art of unduly rapid blood clearance rates can be solved by a recombinant gelatin-like protein having an isoelectric point less than 8. Reconsideration and withdrawal of the provisional double patenting rejection are respectfully requested.

***Claim Rejections - 35 U.S.C. §112, Second Paragraph, Indefiniteness***

Claims 5, 7, 13, 20 and 22 were rejected as being indefinite, on the ground that "no particular sequence is disclosed". Applicant is unaware of any requirement to recite a "particular sequence" in a claim, even in a claim that calls for a recombinant protein. No such sequence recitation is believed necessary to determine the numbers of positively and negatively charged amino acids defined in claim 5 or the locations of amino acid replacements defined in claims 7 and 22. Such limitation would unduly narrow the scope of protection to which he is entitled, in applicant's view. Thus, claims 5, 7, 13, 20 and 22 are believed definite as written, in light of applicant's specification, as will now be explained.

Claim 5, which is dependent on amended claim 1, relates to a composition comprising a recombinant gelatin-like protein comprising Gly-Xaa-Yaa triplets and (the monomer) having a molecular weight of 10,000-50,000 Dalton, and an isoelectric point of less than 8, and wherein at pH 8 the number of negatively charged amino acids minus the number of positively charged amino acids is at least 2 which is to say that there are at least 2 more negatively charged amino acids than positively charged amino acids.

While claim 5 covers a variety of proteins, it will not be indefinite to one skilled in the art because the claim is clearly delimited by multiple structural features, for example, the MW of the monomer, the Gly-Xaa-Yaa motif, and the particular defined isoelectric point. The number of negatively charged amino acids (glutamic acid and aspartic acid) compared to neutral (glutamine and asparagines) and positively charged amino acids (lysine and arginine) may vary, but claim 5 specifies that there should preferably be at least 2 more negatively charged amino acids than positively charged amino acids (see page 10, lines 18-22 and page 14, lines 26-29). A skilled person can easily determine the number of positively and negatively charged amino acids of a given recombinant protein meeting the claim requirements simply by counting the. Similar considerations apply to claims 13 and 20.

Similarly, with regard to Claim 7, the location of replacement of neutral amino acids (glutamine and asparagines) by negatively charged amino acids (glutamic acid and aspartic acid) in an amino acid sequence of a natural collagen protein is determined by the position of the neutral amino acids in the natural protein and no particular sequence need be disclosed. As required by the claims, the number of replacements should be sufficient to obtain an isoelectric point of less than 8. Similar considerations apply to claim 22.

Accordingly reconsideration and withdrawal of the indefiniteness rejections are respectfully requested.

***Claim Rejections - 35 U.S.C. §112, First Paragraph, Written Description***

Claims 1-7, 9-14, 18-22, 24-27 and 31-32, namely those presently pending claims which do not recite a specific SEQ ID NO:, are rejected as failing to comply with the written description requirement.

The Applicant respectfully disagrees. In the first place, the Office's restatement of case law is not complete and consequently may be misleading. In *Regents of the University of California v. Eli Lilly* the Federal Circuit, citing *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) stated that:

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention.

Thus, the dictum applied to DNA whereas applicant claims a recombinant protein and significantly one of the various ways in which a precise definition can be provided include the physical properties, which element was a significant omission from the Office's reference to this case. Furthermore, Applicant's written description is clearly not a "mere wish or plan".

Office practice regarding the written description requirement can be found in the MPEP (8<sup>th</sup> ed. Rev. 2), a relevant portion of which is set forth below:

**2163.02 Standard for Determining Compliance With the Written Description Requirement**

The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an

applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). (*Underlining added.*)

These requirements are believed amply met by applicant as will now be explained.

The claims as previously amended, are limited, *inter alia*, to the presence in the recited recombinant gelatin-like protein of the distinctive Gly-Xaa-Yaa triplets which are characteristic of gelatin and gelatin-like proteins.

Further, it is submitted that the Applicant had possession of the claimed invention, as shown by the specification which clearly describes the structure of the peptides referencing the MW of the monomer, the Gly-Xaa-Yaa motif, and the isoelectric point. Furthermore, the amino acids that may be altered without affecting the colloid osmotic function of the recombinant gelatin-like protein are readily apparent to one skilled in the art. *Any amino acid may be altered as long as the peptide retains the claimed molecular weight of the monomer and an isoelectric point below 8.* See for example Fig. 3, which shows that reducing the IEP from above 8 to below 8 increases the duration of the hyperoncotic effect to more than 6 hours. Similarly, dimers, (HU-2), trimers (HU-3) and tetramers (HU-4) of the monomer, having an IEP below 8 and a

molecular weight of the monomer between 10kDa and 50kDa, show a longer hyperoncotic effect than prior art peptides, see e.g. Fig. 2 compared to Fig. 4 (prior art). Clearly, applicant had possession of the invention.

Furthermore, it was recently held in *Capon v. Eshhar*, 76 USPQ2d 1078 (CA FC 2005) that the “*written description requirement must be applied in context of particular invention and state of knowledge, and there is no per se rule that nucleotide sequence must be recited anew when that information is already known in art*”. Similar considerations apply to the possible peptide sequences which will be apparent to one skilled in the art in light of applicant’s disclosure.

Further evidence of applicant’s possession of the invention as claimed, were any needed, which applicant believes it is not, may be found in the specification which fully describes the essential elements of the claimed recombinant gelatin-like peptides. See for example, page 5, lines 11-17 and lines 23-32; page 7, lines 27 to page 8, line 20; and the whole of page 10. Reconsideration and withdrawal of the rejection based on the written description requirement are respectfully requested.

#### ***Claim Rejections - 35 U.S.C. §103(a) Unpatentability***

Turning now to the rejection of Claims 1-28, 31 and 32 as being obvious over Chang et al. in view of Olsen et al. applicant’s invention, as now claimed, is believed clearly and patentably distinguished from the combination of Chang et al. and Olsen et al. or any other reference or combination of references known to applicant.

Specifically neither Chang et al. nor Olsen et al. suggests the problem addressed by applicant’s invention namely that of unduly rapid blood clearance rates of prior plasma expanders. Accordingly, neither reference can, nor does, suggest applicant’s solution to the problem, namely use of a recombinant gelatin-like protein which has, in addition to the other features set forth in applicant’s claims, an isoelectric point of less

than 8. Since neither reference comprehends the problem addressed by applicant, or provide a solution, there can be no motivation in the art to combine Chang et al. with Olsen et al. and doing so would not provide applicant's claimed invention.

Chang et al. disclose recombinant methods for producing collagens, wherein yeasts such as *Pichia pastoris* are mentioned. In all of the 90 pages of text there is one paragraph on page 28 in which a very general remark is made:

"Using the current methods, one could produce a gelatin with the desired gel strength, viscosity, melting characteristic, isoelectric profile, pH, degree of hydroxylation, amino-acid composition, odor, color, etc"

The choice of words (one could...) and the generality of this remark is such that no enabling teaching is provided to the skilled worker by this sentence. It is an empty teaching. It is merely a wish or a plan, an invitation to experiment.

Further, Chang et al. while does elaborate on the subjects of for example viscosity, melting characteristics and degree of hydroxylation there is no explanation of what constitutes a 'desired isoelectric profile' so that this disclosure is vague and unhelpful and certainly does not constitute a teaching that the isoelectric point of the recombinant gelatin should be below 8 for the purpose of providing a low blood clearance rate, as the present inventors have found. Further the term 'profile' is unclear and could be understood to suggest that that the isoelectric point is to vary over the length of the polypeptide. It cannot be construed from the description what would constitute a profile.

Without admission, or being bound by any theory regarding Chang et al.' disclosure, applicant has attempted to calculate the isoelectric points of Chang's exemplified sequences, in an effort to better understand what one skilled in the art might glean from the Chang et al. disclosure, and has arrived at the following data:

| Seq. ID | IEP  |
|---------|------|
| 15      | 11.1 |
| 16      | 10.3 |
| 17      | 9.7  |
| 18      | 10.3 |
| 19      | 7.0  |
| 20      | 5.3  |
| 21      | 5.4  |
| 30      | 3.5  |

As may be seen, these calculations suggest that the peptides disclosed in Chang et al. have a wide variety of isoelectric points. Possibly, other calculations might lead to a different conclusion. Nevertheless, it is believed clear that Chang et al. do not make any selection of an isoelectric point, nor remotely suggest what a desirable isoelectric point would be.

Olsen et al. disclose and claim a method for producing fibrillar collagens as described in column 3 lines 44-55, to which the Examiner refers. In column 4 lines 4-37, also referred to by the Examiner, it is mentioned that it is also possible to produce collagen monomers. Olsen et al however are silent with respect to isoelectric point of recombinant gelatins.

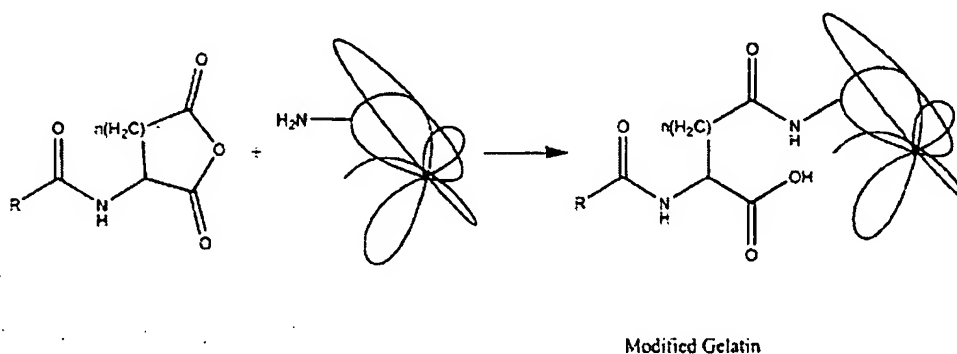
Clearly, however Chang et al. and Olsen et al. might be combed, there is no way a skilled person would arrive at the selection of recombinant gelatin-like polypeptides having an isoelectric point of less than 8 as is required by applicant's claims.

#### *Other Matters*

In the Response to Remarks on page 6 of the Office Action, references to Nahas et al., Hemacel and Plasmion were also mentioned. Since these references were previously distinguished and are not now relied upon to reject any claim of applicant's, it is not clear why they are being further discussed by the Office as they are not at all relevant to applicant's invention as now claimed.



For the record, applicant will nevertheless comment briefly on same. Nahas may appear to disclose gelatin-like materials intended for use as a plasma expander, including some materials having isoelectric points of less than 8. However, Nahas does not disclose materials having the homogeneity and other benefits of a recombinant gelatin. What Nahas does disclose are natural-origin gelatin materials that have been drastically modified to become so-called "modified fluid gelatin" by coupling with succinic anhydride. In this reaction amine groups are replaced by carboxylic groups:



Thus, the number of carboxyl groups is increased at the expense of amine groups, resulting in a lower isoelectric point. The purpose of this modification was to overcome the drawback of high viscosity and high gelation point. In this respect, table IV gives isoelectric points as a physical property of succinylated gelatin, indicating the degree of modification. However, Nahas et al. do not discuss the significance of the isoelectric point and are quite unaware of any desirable isoelectric point for gelatin materials to be used as plasma expanders. The isoelectric points of Hemacel and Plasmion that are referenced are also merely the result of succinylation.

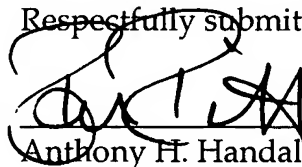
It is believed clear that merely mentioning the isoelectric point of succinylated natural-origin gelatin in Nahas et al., table IV does not suggest any advantage in using recombinant gelatins, that are not modified in the manner of fluid gelatins, and which have an isoelectric point of less than 8.

It is noted that the Hemacel product was clearly distinguished in the response to the Office Action dated June 2, 2004 by amending the claims to specify that the recombinant gelatin recited were not crosslinked by chemical modification, following which rejections based on Hemacel were withdrawn. Plasmion which is also mentioned in Nahas et al. is believed to be the same as Geloplasma® or 'poligelatin'. Geloplasma, hence Plasmion, which is mentioned on page 1 line 29 of the present application. As the record shows, the modified gelatins of Plasmion are similar to those of Hemacel and are not remotely relevant to applicant's invention as now claimed.

In view of the above amendments and the discussion relating thereto, it is respectfully submitted that the instant application, as amended, is in condition for allowance. Such action is most earnestly solicited. If for any reason the Examiner feels that consultation with Applicant's representative would be helpful in the advancement of the prosecution, they are invited to call the telephone number below for an interview.

Respectfully submitted,

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A handwritten signature in black ink, appearing to read 'Roger Pitt', is written over a horizontal line.

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